

# Traditional and emerging cardiovascular risk factors in end-stage renal disease

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**Traditional and emerging cardiovascular risk factors in end-stage renal disease.** Patients with end-stage renal disease face a particularly high risk of cardiovascular disease and total mortality. Part of their increased risk is due to a higher prevalence of established risk factors, such as arterial hypertension, diabetes, smoking, and anemia. Hypertension and diabetes have a very high prevalence in dialysis patients and play a major role in their high mortality and morbidity. Hyperparathyroidism, hyperhomocysteinemia and disordered lipid metabolism represent factors that are peculiarly altered by the uremic state. Inflammatory processes, high sympathetic activity, and the accumulation of an endogenous inhibitor of NO synthase (ADMA), have recently emerged as cardiovascular risk factors of paramount importance. Sleep apnea has been linked with nocturnal hypertension and could be implicated in the high prevalence of concentric hypertrophy of the left ventricle in these patients. Hypertension control, as well as appropriate treatment of anemia and cessation of smoking, constitutes a fundamental area of intervention in dialysis patients. It appears possible that, in the near future, control of chronic inflammatory processes of high sympathetic activity and endothelial dysfunction will further help to curb the exceedingly high cardiovascular mortality of patients on chronic dialysis treatment.

Cardiovascular morbidity and mortality in patients with end-stage renal disease (ESRD) is a problem of epidemic dimension [1]. In the United States Renal Data System, cardiovascular mortality is five times higher in very elderly patients (>85 years) than in coeval controls in the general population. The difference in cardiovascular mortality between the dialysis population and the general population is inversely related to age, and in the younger cohorts (25 to 35 years), such differences reach an astonishing rate of 500 times higher [2].

The main causes of the high cardiovascular mortality in ESRD are represented by ischemic heart disease (IHD), stroke, heart failure, and sudden death (Fig. 1). Three series of factors play an important role in vascular damage and in alterations in left ventricular (LV) mass and

function in chronic renal failure: (1) traditional (Framingham) risk factors (i.e., hypertension, dyslipidemia, smoking, and diabetes); (2) factors peculiar to chronic renal failure (i.e., anemia and secondary hyperparathyroidism); and (3) emerging risk factors, such as inflammation and hyperhomocysteinemia. Other factors that have been recently identified are sleep apnea, high sympathetic activity, and the accumulation of the endogenous inhibitor of NO synthase asymmetric dimethyl arginine (ADMA). Cardiovascular risk is particularly high in diabetic uremics. The issue of cardiovascular risk in diabetic patients with chronic renal diseases has been reviewed elsewhere [3] and will not be discussed in this review.

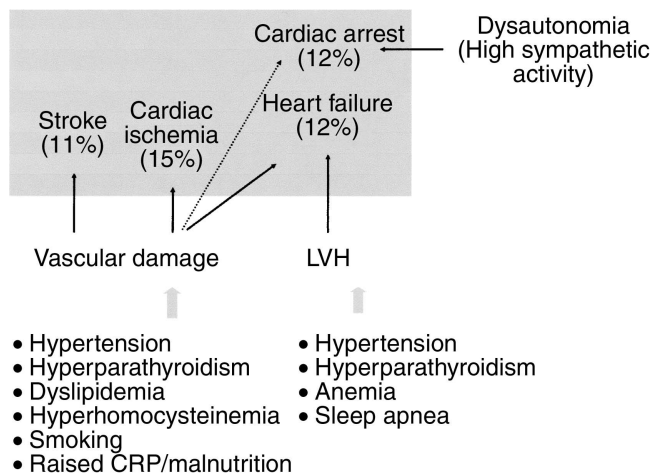
The high cardiovascular risk of the uremic population depends, in part, on the fact that these patients represent a highly selected population in whom traditional risk factors are over-represented. However, traditional risk factors do not fully explain the high cardiovascular risk observed in ESRD.

## **TRADITIONAL RISK FACTORS DO NOT FULLY EXPLAIN THE HIGH CARDIOVASCULAR MORTALITY IN ESRD**

In the general population individual risk can be reliably predicted by using cardiovascular risk calculators. Various calculators are freely available on the Internet. Some calculators are based on the risk equation of the Framingham Cohort, others on an equation based on individual data of the major randomized clinical trials, such as the INDANA project (INDividual Data ANALysis of Antihypertensive intervention trials) [4]. If we calculate, using the INDANA calculator, the expected death rate of a 50-year-old man who smokes, who has had a myocardial infarction, and with a systolic blood pressure of 140 mm Hg and a serum cholesterol of 190 mg/dL (the average BP and cholesterol in most dialysis centers), the predicted risk of death due to a cardiovascular cause in the following five years is 5.4%. The actual death rate in a dialysis patient with identical risk factors is 10 times

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**Fig. 1. Risk factors and intermediate mechanisms implicated in the high cardiovascular risk of end-stage renal disease.**

higher (50%). This difference in risk suggests that in end-stage renal disease traditional risk factors account only partly for the high cardiovascular mortality in these patients.

We will discuss traditional risk factors first and then move to uremia-related and emerging risk factors.

## TRADITIONAL RISK FACTORS

### Hypertension

The role of hypertension in cardiovascular complications in dialysis patients has long been considered an issue of obvious importance. Such a contention was challenged by studies showing that low, rather than high, blood pressure predicts mortality in the dialysis population. In the early 1990s, an extensive meta-analysis of prospective observational studies by MacMahon [5] showed that the risk of cardiovascular events is related linearly to diastolic pressure in the general population, and that such a relationship holds true in the normotensive range as well. It is important to note that patients included in this meta-analysis had no cardiovascular complications before the baseline visit. Of note, the risk reduction associated with lower blood pressure levels in the MacMahon [6] meta-analysis resulted very close to that observed in another meta-analysis dealing with anti-hypertensive drug treatment. In contrast with findings in these meta-analyses, the relationship between blood pressure and risk is J- or U-shaped in several studies in high-risk populations. In retrospective cohort studies based on large hemodialysis databases, the risk of mortality is U-shaped. For example, in a study by Zager [7], mortality was higher among patients who were markedly hypertensive or markedly hypotensive after dialysis, and lowest for those with a systolic blood pressure between 150 and 159 mm Hg. This and other subsequent studies

have caused concern among renal physicians because high blood pressure, rather than low blood pressure, identified dialysis patients with longer survival. Yet, these results come as no surprise because the characteristics of patients being studied dictate the expected relationship between arterial pressure and risk. Thus, the relationship is strong and direct in the McMahon meta-analysis that selected patients without cardiovascular complications at baseline, but is U-shaped in several studies in patients with coronary heart disease. Given the high prevalence of cardiovascular comorbidities in the dialysis population, low blood pressure may be a proxy of compromised cardiovascular conditions. The only prospective observational study in dialysis patients that adequately controlled for cardiac function at baseline (by measuring LV mass and function by echocardiography) showed that a 10 mm Hg mean blood pressure increase was associated with a 44% higher risk of developing congestive heart failure, and that patients with left ventricular hypertrophy or chronic heart failure are at a much higher risk of mortality than patients without these complications [8]. Heart failure lowers blood pressure, and the prevalence of heart failure is very high (about 40%) in both incident and prevalent hemodialysis patients. Thus, low blood pressure is most often a marker of severe cardiac disease rather than a causal risk factor for cardiovascular mortality in these patients (reverse causality). Recent analyses in the Cardiovascular Risk Extended Evaluation (CREED) cohort have substantially confirmed Foley's study, and indicate that the systolic pressure values that minimize cardiovascular risk are in the range between 100 and 150 mm Hg [9].

### Dyslipidemia

Serum cholesterol in ESRD patients is, on average, similar or even lower than that observed in the general population. This phenomenon depends on the fact that malnutrition is pervasive in ESRD. Observational studies in dialysis patients have shown that low, rather than high, cholesterol is a marker of high risk in these patients [10]. These findings have been incorrectly interpreted, indicating that hypercholesterolemia in ESRD should not be a target for intervention. This interpretation is unsound because it ignores the strong evidence accumulated in primary and secondary prevention studies in the general population that indicates a clear benefit of treating hypercholesterolemia. Thus, when present, hypercholesterolemia should be appropriately treated in ESRD patients. A controlled clinical trial testing the effect of atorvastatin in diabetic-uremic patients on dialysis is currently underway (the 4D trial). It is important to note that in this study no major side effects have been noted in over 500 patients treated for almost three years (C. Wanner, personal communication, 2002).

Serum Lp(a) is raised in ESRD, and in cross-sectional

studies it has been associated with coronary heart disease [11]. To date, no follow-up or longitudinal studies testing the prediction power of Lp(a) for incident cardiovascular complications are available. Similarly, there is still no evidence that a selective pharmacologic intervention on Lp(a) reduces the risk of cardiovascular disease. Given the high atherogenic potential of this lipoprotein, such studies are worth pursuing.

### Smoking

Smoking is a risk factor of paramount importance. Recently, it has been implicated in the progression of renal disease in patients with severe hypertension [12]. In the Cardiovascular Risk Extended Evaluation in Dialysis (CREED) study, as many as 118 out of 285 (41%) patients were active smokers. In a detailed echo-color Doppler study of the carotid arteries in this cohort, smoking was a predictor of the number of atherosclerotic plaques, independent of other risk factors [13].

## UREMIA-RELATED CARDIOVASCULAR RISK FACTORS

### Anemia

Anemia has a negative impact not only on quality of life but also on survival. Patients with severe anemia (Ht <27%) have a risk of death 60% higher than patients with moderate anemia (Ht 31% to 33%) [14]. Severe anemia is an important trigger of LVH because intervention studies have demonstrated that correction of anemia induces a partial regression of LVH independent of arterial pressure [15]. The potential role of anemia on cardiovascular risk is further emphasized by recent observations in patients with heart failure and with modest degrees of renal insufficiency [16]. On the other hand, the Normal Hematocrit Trial [17] has shown that in patients at high cardiovascular risk, pursuing the ambitious goal of a normal hematocrit (42%) may increase, rather than decrease, mortality. Although the interpretation of this study is debatable, we should not aim at raising the hematocrit beyond the currently recommended target (33% to 36%) in dialysis patients at high cardiovascular risk. Whether a normal hematocrit affords cardiovascular protection in patients at low risk remains to be established.

### Hyperphosphatemia and hyperparathyroidism

Several mechanistic studies indicate that hyperparathyroidism, hypercalcemia, and hyperphosphatemia can trigger and/or amplify cardiovascular damage in dialysis patients. Observational studies demonstrated that marked hyperphosphatemia (>7.8 mg/dL) is associated with increased mortality [18]. More recently, it has been shown that a relatively less pronounced degree of hyperphosphatemia (>6.5 mg/dL) predicts incident cardiovas-

cular complications [19]. These observations are important mostly because a very recent intervention study reported that controlling hyperphosphatemia and avoiding the administration of calcium carbonate reduces the progression rate of vascular calcifications in the aorta and in coronary arteries, as well [20].

## EMERGING RISK FACTORS

### Homocysteine

Homocysteine is a sulfur amino acid whose metabolism depends on vitamin B<sub>12</sub> and folic acid. The plasma levels of homocysteine are markedly raised in dialysis patients, and high homocysteine levels have been associated with high cardiovascular morbidity in two cohort studies [21, 22]. High-dose folate (5 to 15 mg/day) reduces the serum concentration of homocysteine, but there are no prospective studies showing that lowering serum homocysteine reduces cardiovascular morbidity and mortality.

### C reactive protein

Inflammation as measured by CRP is considered a process of primary importance in the pathogenesis of atherosclerosis and of major cardiovascular complications in the general population [23]. In dialysis patients, CRP is a strong predictor of death and cardiovascular complications [24]. Although CRP is also directly involved in cardiovascular damage, its strong prediction power for adverse cardiovascular events depends on it being a risk marker, rather than a causative risk factor. Factors responsible for high CRP in patients with ESRD are not completely understood. High CRP has been related to increased serum levels of anti-*Chlamydia* antibodies [25], but it is still uncertain if *Chlamydia* infection contributes to atherosclerosis in dialysis patients. Dialysate contamination has been proposed as a likely factor, but serum CRP increases in the early phases of chronic renal failure, well before starting chronic dialysis treatment. Inflammation is a modifiable risk factor. Aspirin induced a marked decrease in the incidence rate of coronary events in the large cohort of apparently healthy subjects enrolled in the Physician's Health Study [26], and lovastatin (a drug which lowers cholesterol and possesses anti-inflammatory properties) prevents cardiovascular events in patients with high CRP independent of its effect on serum cholesterol [27].

## OTHER EMERGING RISK FACTORS

### Asymmetric dimethyl arginine (ADMA) and cardiovascular damage in ESRD

NO production is reduced in patients with moderate to severe renal failure, a phenomenon that is mainly attributed to the accumulation of the endogenous inhibi-

tor of NO synthase, ADMA [28]. On the other hand, it is well demonstrated that endothelial dysfunction is a pervasive phenomenon in patients with chronic renal diseases. This phenomenon may influence later morbidity and mortality from large vessel atherosclerotic disease and LVH.

It has been argued that it is unlikely that ADMA exerts meaningful biologic effects at the plasma concentration measured *in vivo* in humans [29]. Although there is no conclusive proof that ADMA interferes with the cardiovascular system in uremic man *in vivo*, most hemodynamic studies performed so far are compatible with the hypothesis that NO synthase inhibition is implicated in the endothelial dysfunction of dialysis patients. Furthermore, cross-sectional [30] and prospective studies [31] have shown that plasma ADMA concentration is strongly associated to atherosclerotic complications and predicts incident cardiovascular events in these patients. Extensive atherosclerosis and LVH represent the main components of the high risk of uremic patients. Therefore, the fact that ADMA is an independent, high-ranking correlate of carotid atherosclerosis [32] and LV concentric hypertrophy [33] also suggests that this substance is an important factor, mediating a process which may result in important clinical sequels ranging from heart failure to coronary and cerebrovascular complications.

### **Sympathetic overactivity and sleep apnea**

Plasma norepinephrine (NE) in ESRD patients was found to be high in most studies performed between the 1970s and the 1980s [34–36], and on the basis of these studies, chronic renal failure was considered a situation characterized by enhanced sympathetic activity. The interpretation of plasma NE as a marker of sympathetic activity is complex in patients with renal failure because circulating NE represents only a small proportion of the neurotransmitter amount secreted from adrenergic nerve terminals, and because these patients display metabolic alterations which may alter the plasma concentration of this substance. The undisputed standard for the assessment of sympathetic activity is microneurography. This technique has convincingly demonstrated that sympathetic activity in dialysis patients is increased [37], and that this increase is even more consistent than it emerged from early studies based on plasma NE measurements.

Left ventricular hypertrophy is an adaptive process aimed at minimizing ventricular wall stress. Several factors, including hypertension and altered circadian arterial pressure profile, may influence this process in patients with renal diseases. The evidence that the sympathetic system is involved in the progression of cardiovascular structural alterations such as left ventricular hypertrophy and arterial remodeling in the general population is now substantial [38]. Norepinephrine promotes myocardial cell hypertrophy *in vitro*; *in vivo*, sustained sympathetic activ-

ity generates myocardial hypertrophy by mechanisms only partly dependent on raised arterial pressure. In line with observations suggesting that hypertension only in part accounts for raised LV mass, we have recently reported that the link between the muscular component of LV mass (mean wall thickness) and plasma NE is largely independent of arterial pressure and other risk factors [39]. Furthermore, we have also provided evidence that high plasma norepinephrine in dialysis patients is an important trigger for cardiovascular events [40].

The cause of sympathetic overactivity in renal failure is still poorly defined. An alteration in afferent neural inputs in diseased kidneys is a possible culprit because sympathetic nerve activity decreases in uremic man after bilateral nephrectomy [37]. Nocturnal hypoxemia triggered by sleep apnea seems to be another likely cause. Sleep apnea is very frequent in ESRD (about 30%), and nocturnal hypoxemia has been associated with a nocturnal increase in arterial pressure [41], concentric hypertrophy [42], and adverse cardiovascular outcomes in dialysis patients [43]. Nocturnal hypoxemia triggers a marked increase in sympathetic activity that outlasts hypoxemic episodes. Thus, it appears possible that the high sympathetic tone in ESRD at least in part depends on the high frequency of sleep apnea and nocturnal hypoxemia in this population. Whatever the explanation for high sympathetic tone in patients with chronic renal failure may be, this factor is clinically important because it can be modified by using anti-adrenergic drugs. It has been shown that carvedilol reduces left ventricular volume and improves systolic function in dialysis patients with ventricular dilatation [44]. Since carvedilol has antioxidant properties, it is difficult to establish whether the favorable effects of this drug depend solely on its anti-adrenergic activity. Yet, this study pragmatically shows that interfering with adrenergic activity may represent an important intervention area.

Reducing cardiovascular risk in dialysis patients is an absolute priority. At this stage we have “evidence-based” options for intervention for some traditional risk factors only. While it is almost undisputable that hypertension is a risk factor to be appropriately treated in dialysis patients, and that those patients should stop smoking, we still don’t know whether normalizing hemoglobin in patients without advanced cardiovascular disease may help to prevent cardiovascular damage. Furthermore, there are still no intervention studies aimed at modifying serum phosphate based on hard end points, or convincing proof that reducing plasma homocysteine reduces cardiovascular risk in dialysis patients. Until now, there has been no study proving that interfering with sympathetic activity or with ADMA may reduce the cardiovascular burden of ESRD. Presently, we should pay more attention at systematically using available cardiovascular treatments (e.g., anti-hypertensive drugs, aspirin, and



statins) after careful consideration of the risk profile of the individual patient, and at treating anemia and hyperphosphatemia wisely; the hard reality remains that patients with compromised renal function still receive less intensive cardiovascular treatment, even in emergency situations like myocardial infarction [45].

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